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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 03/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/614,326	Applicant(s) EDELBERG ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-30,32,33,43,45,48,52-54,56-58 and 69-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-30,32,33,43,45,48,52-54,56-58 and 69-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Note that the Examiner of Record has changed. The Examiner of Record is now Thaian N. Ton of Art Unit 1632.

Applicants' Amendment, filed 1/16/02, Paper No. 8, has been entered. Claims 31, 34-42, 44, 46, 47, 49-51, 55, 59-68 have been cancelled. Claims 26, 28, 29, 32, 33, 48, 52, 58 and 790 have been amended. Claims 72-77 have been added.

Claims 26-30, 32, 33, 43, 52-54, 56-58, 69-77 are currently pending and under examination.

Any rejection made of record in the prior Office action, mailed 5/10/01, Paper No. 6, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 26-30, 32, 33, 43, 52-54, 56-58, 69-71 under 35 U.S.C. 112, first paragraph is maintained, for reasons of record advanced on pages 3-8 of the prior Office action. Newly added claims 72-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the expression of the β_2AR gene *in vitro* in myocardiac cells by the transfection of the

construct, and being enabling for the increased rate of contraction of the transduced cells *in vitro*, does not reasonably provide enablement for correction of cardiac dysfunction in mammals, and specifically humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of introducing a biological pacemaker into the atrial chamber or sinoatrial node region of a mammalian heart for regulating cardiac pacemaking activity.

Applicants argue that the claims have been amended to the regulation of heart rate or contractility of cells, and that data enabling this aspect is disclosed in the "Examples" section of the specification [see p. 5 of the Response].

In response it is noted that with regard to claim breadth, the standard under 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account, because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, in light of the specification's disclosure that the biological pacemaker of the instant invention can be used for the treatment of an individual suffering from cardiac conductive tissue incompetence, and in light of the

claimed invention, the disclosed use of the claimed invention would be directed to therapeutic outcomes using the claimed biological pacemaker.

Applicants' argue that they have provided support for the expression of the β_2AR gene both *in vitro* and *in vivo* [see p. 6, 1st paragraph of the Response]. Applicants further argue that the claimed invention does not encompass the gene therapy methods as described in the Office action, and that the methods of cell grafting and direction injection predictably allow for the expression of genes to upregulate heart rate or alter cardiac rhythm [see p. 6-8 of the Response]. However, as noted *supra*, the intended use of the claimed invention is directed to methods of treatment, and the specification has failed to provide a correlation to *therapeutic* levels of expression of the β_2AR gene in an *in vivo* setting in a subject suffering from, for example, cardiac conductive tissue incompetence. The mere showing of the upregulation of heart rate or altered cardiac rhythm does not provide sufficient teachings to enable the claimed invention. Furthermore, the claims broadly read on <u>any</u> mode of administration of the cardiac pacemaker [see, for example, claims 26 and 33]. For example, claim 33, broadly reads on "introducing" a biological pacemaker into the sinoatrial node region of the mammalian heart. Note that claim is not limited any particular mode of administration. As such, the Examiner has appropriately provided teachings concerning the general state of the art of gene therapy, with particular regard to its unpredictability [see pp. 4-6 of the prior Office action].

Note further, that the art cited in the prior Office action [pp. 4-6], clearly indicates the unpredictable status of the gene therapy art, in general sense, and in particular, as it specifically pertains to cardiac/myocardial gene therapy. Although specific vectors, promoters, genes and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy, as a broad-based art, is clearly unpredictable in terms of achieving levels of duration and expression of a particular gene of interest (in this case, the β_2AR gene) which results in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed. In the instant application, a correlation cannot be drawn for the reasons advanced on pages 4-6 in the prior Office action. As established by the state of the art of gene therapy, note that therapeutic expression is not an inherent feature in methods of either *in vivo* or *ex vivo* gene transfer involving expression of a protein of interest. In fact, the lack of a therapeutic response in many gene therapy protocols contributes to the unpredictable and undeveloped status of the art of gene therapy.

Applicants argue that the use of animal models to be indicative of likely success in humans or other animals, and state that the Yorkshire pig was chosen for its anatomic and physiologic similarity to the human cardiovascular system [see p. 8, 2nd full paragraph]. The Examiner notes that the Yorkshire pigs disclosed by the specification were not an art-recognized model for any disease involving cardiac

conductive tissue incompetence. As such, Applicants have not provided a correlation between the disclosed pig injected in the heart with the claimed pacemaker and a therapeutic outcome for an individual suffering from cardiac conductive tissue incompetence.

Note also, that the issue of "correlation" is dependent upon the state of the art at the time of the invention. MPEP 2164 discusses that if one skilled in the art cannot readily anticipate the effect of a change within a subject matter to which the claimed invention broadly pertains, then there is a lack of predictability in the art. Thus, what is known in the art provides evidence as to the question of predictability.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters [advanced on pages 6-8 of the prior Office action] for achieving β_2AR gene therapy, the lack of direction or guidance provided by the specification to carry out β_2AR gene therapy, as broadly claimed, involving any route of administration, vector, or subject, the absence of working examples for the demonstration or correlation to achieving therapeutic β_2AR gene expression *in vivo*, the breadth of the claims directed to any route of administration, vector, or subject, as well as the unpredictable and undeveloped state of the art with respect to gene therapy, it would have required undue experimentation for one skilled in the art to make and/or use the claimed pacemaker and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-30, 32, 33, 43, 52-54, 56-58, 69-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26, 56 and 70, as written, are unclear. The claims recite the term, "cellular-based cardiac biological pacemaker". It is unclear what "cellular-based" encompasses, for example, the claims read on a cell that has been transduced *in vivo*. Claims 27-30, 32, 33, 43, 45, 48, 52-54 depend on claim 26; claims 57, 58 depend from claim 56; claims 71-75 depend from claim 70.

Claim 76, as written, is confusing. The claim recites that the cell is transfected with one gene that increases the rate of contraction of the cell. It is not expected that all cells would contract. Clarification and/or amendment is requested. Claim 77 depends from claim 76.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 26, 28, 29 and 43 is maintained under 35 U.S.C. 102(b) as being anticipated by Milano *et al.* (for reasons of record advanced in prior Office action, p. 8-9).

Milano *et al.* teach a construct that allows for the stable expression of β_2AR in the murine heart. Applicants argue that the teachings of Milano *et al.* would not be enabled in the methods described by Applicants' amended claims [see p. 9, last paragraph of the Response]. In response, it is noted that the claims are directed to products, not methods. Further, the claims recite the term, "cellular-based" which encompasses cells that contain the claimed construct both *in vivo* (as Milano *et al.* teaches) and *in vitro.* Applicants further argue that Milano *et al.* do not teach the introduction of a construct by direct injection [see p. 9-10 of the Response]. It is noted that the amended claims do not limit the invention to direct injection.

Accordingly, Milano *et al.* anticipate the claimed invention.

The prior rejection of claims 26, 28, 30, 43 is maintained. Newly added claims 76 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaudin *et al.* (for reasons advanced in the prior Office action, p. 9).

The claims are directed to a cellular-based cardiac biological pacemaker comprising at least one cell transfected or transduced with at least one gene that upregulates heart rate or alters cardiac rhythm suitable for localized gene

expression in mammalian cardiac atrial tissue. The claims are directed to a cell transduced or transfected with at least one gene that increases the rate of contraction of the cell, and in further embodiments, the gene is selected from a β_1AR gene, β_2AR and $G_{s\alpha}$ gene.

Gaudin *et al.* teach that alterations in β-adrenergic receptor-G_s-adenylyl cyclase coupling underlie the reduced catecholamine responsiveness that is found in human and animal models of heart failure. Gaudin *et al.* teach a construct comprising a $G_{s\alpha}$ gene that was overexpressed in the hearts of transgenic mice [see *Abstract*]. Further, Gaudin *et al.* teach that there was an accelerated activation of adneylyl cyclase activity in the transgenic mice expressing increasing levels of the $G_{s\alpha}$ protein [p.1682, paragraph 5, lines 14-16]. Gaudin *et al.* teach that the small change in the content of $G_{s\alpha}$ protein can impact receptor-G_s coupling and the rate of adenylyl cyclase activation in the heart. Gaudin *et al.* teach that increase in catecholamines can cause an increase in heart rate, and the transgenic mice produced can be used to study receptor activation *in vivo* [see p. 1683, 1st column, 2nd paragraph].

Applicants argue that the teachings of the expression of $G_{s\alpha}$ in transgenic mice by Gaudin *et al.* would not be enabled to use such a construct for the methods described by Applicants' amended claims because the claims are directed to a cellular-based cardiac pacemaker, and introduction of a construct by direct injection [see p. 10 of the Response]. It is noted that the claims recite "cellular-based" which

reads on cells that contain the claimed construct both *in vivo* (as Gaudin *et al.* teaches) and *in vitro*. Further, it is noted that the amended claims do not limit the invention to direct injection.

Accordingly, Gaudin *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Deborah Crouch

TNT

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